IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Paul A. Dickinson and Simon J. Warren
Application No.: 10/668,840
Filing Date: September 23, 2003
For: Aerosol Composition

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Examiner: Sharmila S. Gollamudi

Assistant Commissioner for Patents
Washington DC 20231

Sir:

DECLARATION OF PAUL A. DICKINSON, Ph.D. PURSUANT TO 37 C.F.R. § 1.131

I, Paul A. Dickinson, Ph.D., hereby declare the following:

(1) I, together with Simon J. Warren, Ph.D., invented the subject matter claimed in the above-referenced patent application.

(2) Dr. Warren and I invented the claimed subject matter prior to 16 March 1998.

(3) As evidence of our prior invention of the claimed subject matter, enclosed herewith is a true and complete copy of a letter (with enclosure) sent to me by Ms. Susan Thomas of Carpmaels & Ransford prior to 16 March 1998. Ms. Thomas was acting as our patent counsel and prepared the patent application filed 3 April 1998 as GB9807232.5. Enclosed with Ms. Thomas' letter was a nearly finalized draft of that patent application.

(4) The draft application enclosed with Ms. Thomas' letter clearly shows that the invention that is the subject of the present application was made prior to 16 March 1998.

(5) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 4th May 2006

Paul A. Dickinson, Ph.D

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YOUR REF

OUR REF G22510P: PNH/SMT/ae

Dear Dr Dickinson,

Re: Proposed new Patent Application for Metered Dose Inhaler

Thank you for your letters of 10th, 17th, 23rd and 24th February and 4th March 1998.

I enclose an amended draft of the patent specification which has been revised having regard to your comments, the new data and our telephone conversations. In particular the specification now includes the very useful comparative data which serves to highlight the benefits of the present invention, the data illustrating alternative components of the invention, and a section to distinguish between acceptable flocculation and undesirable aggregation.

In view of the fact that the rationale of the present invention depends on the size of the particulate materials present it is important to state clearly what is required in technical terms to achieve the beneficial outcome of the invention. I have set the lower limit of the second particulate material at 15 μm having regard to Example 15.

Please read the enclosed draft specification carefully and let me have any comments you may have. I look forward to receiving your comments and instructions to proceed with filing the application as soon as possible.

You asked in your letter of 17th February 1998 whether a fast track scheme exists with regard to processing a filed patent application. There are ways of fast-tracking United Kingdom patent applications. However, in the absence of a specific reason for doing so (e.g. you are aware of an infringer) I would not recommend fast tracking the application at this stage.

Within 12 months of filing of the UK patent application, applications in respect of other countries can be filed which are credited with the UK filing date for subject matter contained in the original UK patent application. It is also possible to add new subject matter such as new embodiments, preferred ranges etc. at this stage, although they will

only be accorded the date of filing of the application in which they first appear. Additional UK patent applications can be made at any time during the next 12 months directed to the new data, and the content of the applications combined at the foreign filing stage. It is important therefore not to disclose any improvements or alternatives to potential licensees until they are included in any further patent application.

This 12 month period is thus a valuable time to refine the invention if required, to make an assessment of the strength and breadth of any potential patent(s), especially having regard to the results of the UK Patent Office novelty search, and hence make a decision as to how widely to file the patent application elsewhere, and even to find a licensee to fund the foreign filing costs, which can be considerable.

Once the present application is filed at the UK Patent Office you can in principle disclose the contents of the specification to potential licensees without such disclosure adversely effecting the validity of any patent which may eventually be granted on the original application. However, I would caution that any public disclosure of the subject matter of the application could be citable against any subject matter added to the application over the next 12 months. Accordingly, if there is any possibility that the scope of the invention (particularly as defined in the claims) will be refined or modified over the next 12 months, I recommend that the subject matter of the present application is <u>not</u> published and is only disclosed (e.g. to potential licensees) under a written confidentiality agreement.

If you decide to continue with the application at the 12 month stage it will automatically be published by one or more of the patent offices you have selected six months later. Once published, a variety of rights, depending on the country, accrue to the application with regard to third parties using your invention without your permission. In some countries it can at this stage be possible to request accelerated prosecution of the application if you are aware of a third party actually using your invention without your permission.

I trust that the above answers your question. If you require any further explanation about the patent procedure and how it effects you please let me know.

Finally, I would emphasise that the patent application has not yet been filed. I look forward to receiving your comments on the amended specification and your instructions to proceed with filing the application as soon as possible.

Please do not hesitate to contact me if you have any queries.

Yours truly,

Susan Thomas

Susan Thomas,
<u>for CARPMAELS & RANSFORD</u>

cc Dr H. Jones + enc.

Aerosol Composition

The present invention relates to an aerosol composition. In particular the present invention relates to an aerosol composition in the form of a suspension comprising liquid propellant and particulate material.

Effective use of an aerosol composition in the form of a suspension usually requires the suspension to comprise a uniform dispersion of particulate matter in order to ensure the production of an aerosol of known components in known amounts. Inhomogenous dispersions can occur due to poor dispersibility of the particulate matter in the propellant and/or a tendency of the particulate matter to aggregate and possibly even to aggregate irreversibly.

Aerosol compositions comprising particulate matter in the form of a suspension can be used for the delivery of a number of active agents. A particular application comprises pharmaceutical suspensions for administration of a drug in particulate form.

An example of a pharmaceutical application of a particulate-containing aerosol composition is inhaler suspensions. Inhaler suspensions are used for delivery of a particulate medicament to the lungs or upper airway passages. Suitably the suspension is contained in a container fitted with a metering valve. A known dose can thus be administered on each occasion of use. Such containers can be convenient to use and are readily portable.

Such a metered dose inhaler conventionally consists of a pressurised container which has a metering valve of fixed volume to measure individual doses of a suspension of medicament held in the container. In order to ensure the administration of an accurate dose of suspended particulate medicament it is essential that the suspension is consistently and homogeneously dispersed. The suspension conventionally comprises medicament particles dispersed in a liquefied gas which in use acts as a propellant. On depressing the valve stem of the metering valve the propellant fraction of the metered dose rapidly vaporises so as to aerosolise the suspended particulate medicament which is then inhaled by the user.

Traditionally, chlorofluorocarbons such as CFC-11, CFC-12 and CFC-114 have been employed as propellants in metered dose inhalers. A particulate medicament intended for pulmonary administration needs to have a particle size with a median aerodynamic diameter between about 0.05 μm and about 11 μm. This range of size of medicament particle is important in inhalers. Larger particles will not necessarily or readily penetrate into the lungs and smaller sized particles are readily breathed out. However, particles between about 0.05 μm and about 11 μm can possess a high surface energy and can therefore be difficult to disperse initially in the propellant, and once dispersed can exhibit a tendency to aggregate undesirably and rapidly, leading eventually to irreversible aggregation of the particles. In the case of CFC as a propellant this problem was overcome by the addition of a surfactant soluble in the CFC which coats the medicament particles and prevents aggregation by steric hindrance. In practice medicament particles were homogenised in the liquid CFC-11 with the inclusion of a propellant soluble surfactant such as lecithin, oleic acid or sorbitan trioleate. The resulting bulk suspension was dispensed into individual metered dose inhalers and a high vapour pressure propellant such as liquefied gas CFC-12/CFC-114 added. Such arrangements proved satisfactory in use, although the added surfactant could adversely affect the perceived taste of the inhaler in use. For example oleic acid could impart a bitter taste.

In recent years the detrimental effect of chlorofluorocarbons on the ozone layer in the earth's stratosphere has become apparent. The continued use of CFC has therefore become unacceptable and in some instances has been banned by local regulations.

Alternative propellants which share some similar physical properties to those of previously used CFC propellants and which have been suggested for use in metered dose inhalers are hydrofluoroalkanes, notably HFA-134a and HFA-227. Problems however exist on attempting to formulate the hydrofluoroalkanes into an aerosol composition such as an inhaler suspension. Firstly, the acceptable surfactants employed in CFC based suspensions are not sufficiently soluble in hydrofluoroalkanes to prevent irreversible aggregation of the particulate medicament occurring. Secondly, neither HFA-134a nor HFA-227 is a liquid at an acceptable temperature so that bulk

homogenisation with particulate material prior to filling into individual pressured containers is only possible if carried out under pressure.

A number of proposals have been made in an attempt to employ hydrofluoroalkanes as the propellant in pressurised metered dose inhalers for example a patent specification (WO 92/06675) in the name of Minnesota Mining and Manufacturing Company suggests the use of non-volatile co-solvents to modify the solvent characteristics of the hydrofluoroalkane propellant and thereby increase the solubility and hence permit the use of the surfactants traditionally employed in CFC based metered dose inhalers. The presence of the co-solvent however may result in less desirable aerosol properties. Moreover the alcohol non-volatile co-solvents suggested can impart an unpleasant sharp taste.

Patent specifications (WO 91/11173 and WO 92/00061) in the name of Fisons suggests the use of alternative surfactants which are sufficiently soluble in HFA-134a and HFA-227. The surfactants proposed however may present toxicity problems in use. Extensive and expensive toxicity studies are therefore required before the pharmaceutical regulatory authorities will permit their inclusion in a product intended for human use.

Other proposals to provide a metered dosed inhaler employing hydrofluoroalkane are found in patent specification no. WO 92/08477 in the name of Glaxo Group Limited and patent specification no. EP 372777 in the name of Riker Laboratories, Inc. Neither proposal has been found satisfactory.

A need therefore exists to provide an aerosol composition suitable for use in for example, an inhaler, comprising a suspension of particulate matter in a propellant, which composition has good dispersion characteristics, a reduced tendency to aggregate and can in use be effectively aerosolised.

It is an object of the present invention to provide an aerosol composition including a particulate material suitable for use in for example an inhaler which composition

exhibits both a reduced tendency for the particulate material to aggregate undesirably and ready and homogeneous dispersion of the particulate material.

It is a further object of the present invention to provide an additive comprising a particulate material for use in the preparation of such an aerosol composition.

It is a further object of the present invention to provide a container, such as an inhaler, containing such a composition.

Further objects of the present invention include a method of preparing a container containing such a composition and a method of administering the composition.

According to a first aspect of the present invention there is provided an aerosol composition comprising a propellant and contained therein a first particulate material comprising particles having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material comprising particles having a median volume diameter within the range 15 to 200 μm.

The inclusion of a second particulate material having a median volume diameter in the range 15 to 200 μm in combination with the first particulate material having a median aerodynamic diameter in the range 0.05 to 11 μm has unexpectedly been found to enhance dispersion and to reduce particulate aggregation, leading to a reduced risk of irreversible aggregation, whilst still permitting good aerosol performance of the suspension in use. The result is unexpected as *prima facie* the inclusion of extra insoluble solids had been considered to be inappropriate leading to less desirable aerosol characteristics and poor valve performance. The present invention can thus permit the delivery of particulate material at a known and consistent concentration.

Although we do not wish to be bound by any theory we believe that the presence of the second particulate material having a median volume diameter in the range 15 to 200 μm reduces the risk of irreversible aggregation of the first particulate material as the larger particles are unable to pack sufficiently close together to permit packing of particles in

the primary energy minimum. By "irreversible aggregation" we mean aggregation of particles which cannot be dispersed by hand held shaking.

To reduce further the risk of unwanted packing of the particles the second particulate material having a median volume diameter in the range 15 to 200 μm preferably constitutes particles that are substantially spherical in shape and/or are irregularly shaped.

Within the aerosol composition the first and second particulate materials are believed to be present as either a simple admixture or with some or all of the smaller first particulate material particles interacting with the larger particles of the second particulate material. The presence of the second particulate material can thus help to prevent non-specific adsorption of the first particulate material to the inside surface of a container containing the aerosol composition.

The presence of the second particulate material in the propellant can lead to flocculation i.e. loose association of the suspended particles into a fluffy floc. Flocculation differs from irreversible aggregation in that it occurs in the secondary energy minimum and is dispersible by hand held shaking. Flocculation of the second particulate material can occur in the propellant either in the absence or in the presence of the first particulate material. Where flocculation occurs in the absence of the first particulate material, the equivalent composition containing additionally the first particulate material can surprisingly inhibit the flocculation occurring. Where flocculation of the second particulate material does however occur in the propellant in the presence of the first particulate material it is not detrimental to the present invention as it can be removed by hand held shaking prior to use of the aerosol. It may moreover even be beneficial in preventing irreversible aggregation in the primary energy minimum.

By "volume diameter" is meant the diameter of a sphere having the same volume as the particle. The second particulate material is selected according to its volume diameter as it is the physical bulk of the second particulate material which is believed to be important in determining the properties of the suspension.

By "aerodynamic diameter" is meant the volume diameter multiplied by the square root of the ratio of the particle density (g cm^{-3}) to the density of a particle with same volume diameter having a density of 1 g cm^{-3}. The first particulate material is thus selected according to its volume diameter having the stated consideration for its density. In the definition of "aerodynamic diameter" given above the assumption is made, in keeping with conventional aerosol practice, that the first particulate material can be deemed to be spherical in shape. Moreover, where as is usually the case, the first particulate material has a particle density between about 1 and 2 g cm^{-3} the aerodynamic diameter of the first particulate material is approximately equivalent to its volume diameter

According to another aspect of the present invention there is provided a container containing the aerosol composition according to the present invention, the container including a valve outlet. Suitably the contents of the container are pressurised up to a pressure of 6.895×10^5Pa (100 psig). Preferably the container includes a metered valve outlet capable of delivering a measured dose of suspension in the form of an aerosol. Preferably the container is in the form of an inhaler.

According to another aspect of the present invention there is provided a method for preparing an aerosol composition comprising:-

(a) forming a mixture of a first particulate material comprising particles having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material having a median volume diameter within the range 15 to 200 μm;

(b) dispensing measured portions of respectively said mixture and a propellant into a container; and

(c) sealing the container.

Suitably the container is pressurised and includes an outlet valve, preferably a metered dose dispensing valve.

The mixture of the first particulate material and the second particulate material permits ready dosing of the mixture into the container due to improved flow characteristics compared to the first particulate material in the absence of the second particulate material. Suitably the mixture is dosed into the container before the propellant. The enhanced dispersion characteristics of the mixture in the added propellant permits the omission of the step of providing a homogeneous suspension prior to dispensing into a container. In keeping with conventional procedures for preparing an aerosol the container can be sealed following the dosing of the mixture into the container, with the propellant being subsequently dosed into the container through for example an outlet valve forming a part of a seal.

According to another aspect of the present invention there is provided a mixture of a first particulate material having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material having a median volume diameter within the range 15 to 200 μm.

According to another aspect of the present invention there is provided a use of a particulate material, for example lactose, having a median volume diameter lying in the range 15 to 200 μm to enhance the dispersion characteristics of a particulate material having a median aerodynamic diameter lying in the range 0.05 to 11 μm in suspension in a propellant.

According to another aspect of the present invention there is provided a method of administering a particulate material to a patient in need thereof comprising the patient inhaling an aerosol comprising vaporised propellant and a mixture of an active agent comprising particles having a median aerodynamic diameter lying in the range 0.05 to 11 μm and a second particulate material comprising particles having a median volume diameter lying in the range 15 to 200 μm. In applying the method forces generated by vaporisation of the propellant separate particulate active agent from the mixture such that the active agent is available and suitable for lung deposition after inhalation. The method can be applied orally or nasally.

Preferably the first particulate material has a median aerodynamic diameter within the range 1 to 10 μm, more preferably within the range 1 to 5 μm. Where the present aerosol composition is employed as an inhaler such preferred ranges are optimum for respiratory delivery.

Preferably the second particulate material has a median volume diameter within the range 20 to 125 μm, more preferably within the range 25 to 125 μm, even more preferably within the range 30 to 125 μm, even more preferably still within the range 38 to 125 μm.

Preferably the weight ratio of the first particulate material to the second particulate material lies in the range 1:0.1 to 1:500, the weight being that of the first particulate material and the weight of the second particulate material admixed with the propellant and thus includes any material dissolved in the propellant. More preferably the weight ratio of the first particulate material to the second particulate material lies in the range 1:1 to 1:200, even more preferably within the range 1:5 to 1:50. The actual ratio selected for any particular suspension will depend *inter alia* on the solubility of each of the first and second particulate materials in the propellant, the dosage or usage requirements of the particulate materials and the extent of any interaction between the first particulate material and the second particulate material.

The actual amount and size of each particulate material used will depend *inter alia* on the solubility of each particulate material in the propellant and the type and dose of each particulate material required. Suitably however the aerosol composition comprises 80 to 99.999 wt% propellant, more suitably 90 to 99.9 wt% propellant. The total weight of particulate material employed, measured as including dissolved and undissolved material, is thus suitably 20 to 0.001 wt% with respect to the total weight of the composition, more preferably 10 to 0.1 wt% with respect to the total weight of the composition. The concentration of the first particulate material in the composition, including dissolved and undissolved material, preferably lies in the range 1 to 0.0001 wt%, more preferably in the range 0.5 to 0.005 wt% with respect to the total weight of the composition.

Each of the first and second particulate materials may be partially soluble in the propellant. Preferably the solubility of the first particulate material in the propellant does not exceed 49.9 wt% with respect to the total weight of the substance comprising the first particulate material present. More preferably the solubility of the first particulate material in the propellant does not exceed 10 wt%, even more preferably 1.0 wt% with respect to the total weight of first particulate material present.

Preferably the solubility of the second particulate material in the propellant does not exceed 49.9 wt% with respect to the total weight of the substance comprising the second particulate material present. More preferably the solubility of the second particulate material does not exceed 10 wt%, even more preferably 1.0 wt% with respect to the total weight of the second particulate material present. Low solubility of each of the first particulate material and the second particulate material is preferred in order to avoid stability problems such as the risk of particle growth due to Ostwald ripening.

Preferably the ratio of the density of the second particulate material to the density of the propellant lies in the range 0.9:1 to 1:1.1. Too large a density difference between the density of the second particulate material and the density of the propellant is preferably avoided. The optimal density difference can be ascertained in each instance, particularly having regard to the ambient temperature effecting the density of the propellant and any tendency of the second particulate material to flocculate in the presence of the first particulate material. When not equal to the density of the propellant the density of the first particulate material and the density of the second particulate material are suitably both either more than or less than the density of the propellant. Should the first and second particulate materials exhibit any tendency to sediment or cream (i.e. float) their uniform dispersion in the propellant can thus be more readily achieved.

The substance comprising the second particulate material is suitably chemically unreactive with respect to the first particulate material. The present aerosol composition can be in the form of a pharmaceutical composition. Where the first particulate material is a medicament, the second particulate material preferably does not modify the biopharmaceutical profile of the medicament comprising the first particulate material.

The second particulate material can comprise one or more active or inactive agents or a mixture thereof, for example it can comprise one or more pharmacologically inert substances, one or more pharmacologically active substances, one or more flavour imparting substances or a mixture thereof.

Where the present aerosol composition is intended for use as an inhaler, the second particulate material can for example comprise a pharmacologically active substance for oral administration. Preferably it comprises a substance to impart a palatable flavour such as a sweet flavour to the inhaler.

Where the first particulate material is a medicament, the second particulate material should be acceptable for administration to a human. Preferably it will be a substance which already possesses regulatory approval and has a desirable safety profile. For example where the present aerosol composition is intended for use as an inhaler the second particulate material may already posses regulatory approval for use in pulmonary administration. The second particulate material selected should preferably be relatively inexpensive and readily available.

Suitable substances for use as the second particulate material in at least an inhaler may be selected from lactose, glucose, sorbitol, mono-, di-, tri-, oligo- and poly-saccharides, amino acids, di-, tri-, oligo- and poly-peptides, mixtures thereof and physiologically acceptable derivatives, forms, salts and solvates thereof. Preferably the second particulate material is selected from lactose, glucose and leucine and mixtures thereof. The material can be in any appropriate form, for example lactose can be α-lactose, β-lactose, anhydrous lactose, or any crystalline form of lactose or any mixture thereof.

Where the first particulate material is a particulate medicament suitable for oral or nasal inhalation and the aerosol composition is intended for use as an inhaler, examples of suitable particulate medicaments for use in the treatment and prevention of asthma and other conditions associated with reversible airways obstruction include either alone or in any combination:

(i) salbutamol, salbutamol sulphate, mixtures thereof and physiologically acceptable salts and solvates thereof,

(i) terbutaline, terbutaline sulphate, mixtures thereof and physiologically acceptable salts and solvates thereof,

(iii) budesonide and physiologically acceptable solvates thereof,

(iv) triamcinolone acetonide and physiologically acceptable solvates thereof,

(v) ipratropium bromide and physiologically acceptable salts and solvates thereof, and

(vi) corticosteriod or bronchodilator.

Other examples of particle medicaments suitable for oral or nasal inhalation by means of the present aerosol composition include:

(vii) peptides, proteins, nucleic acids and derivatives thereof for use in the treatment and prevention of disease states,

(viii) insulin, calcitonin, growth hormone, lutenising hormone release hormone (LHRH), leuprolide, oxytocin and physiologically acceptable salts and solvates thereof for use in the treatment and prevention of disease states including diabetes, and

(ix) any pharmacologically active particulate medicament having a median aerodynamic diameter within the range 0.05 to 11 μm administered in the form of an aerosol.

The dosage requirements for any one medicament will be those conventionally employed in inhalers. For example where the first particulate material is salbutamol for use in relation to asthma the inhaler is employed as required, usually 1 or 2 actuations (i.e. puffs) between 0 and 4 times per day, with a single metered dose comprising 100 mg of salbutamol in a volume of metered liquid propellant between 20 and 150 μl.

The propellant is preferably selected from chlorofluorocarbons, hydrofluorocarbons and mixtures thereof. When the propellant is a chlorofluorocarbon such as CFC-11, CFC-12, CFC-114 and/or CFC-141 the present invention can provide a suspension that obviates the need for the addition of unpalatable, or possibly even mildly toxic, surfactant. Alternatively the propellant can comprise hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227) and mixtures thereof. The combination of the first particulate material with the second particulate material both reduces the risk of the first particulate material aggregating undesirably and enhances the dispersement of the particulate medicament in the propellant. In manufacturing individual units of the suspension the increased dispersibility provided by the present invention obviates the need to prepare an initial bulk suspension by a homogenisation step. The combination of the first particulate material and the second particulate material can be readily wetted by and dispersed in HFA propellants in the absence of surfactant or added co-solvent. The suitable dispersion characteristics in HFA displayed by the presently provided combination of particulate materials permits its initial dispersion and any redispersion required following sedimenting or creaming with a small energy input, e.g. hand held shaking.

The present suspension can optionally contain any additional appropriate ingredients, for example pharmacologically acceptable excipients such as a surfactant, flavouring, buffer and preservatives in conventional acceptable amounts.

Embodiments of the present invention will now be described by way of example only with reference to the following Examples and the accompanying figure which is a cross-section of a metered dose inhaler.

The present embodiments relate to an aerosol composition in the form of an inhaler.

Comparative Examples A to T

Examples A to Q are comparative examples and demonstrate the suspension properties of a variety of particulate materials in the absence of a medicament.

Each suspension was assessed visually for its ease of dispersion on hand held shaking, its extent of aggregation and the quality of the suspension.

Ease of dispersion was scored on a scale of good (g), medium (m) and poor (p).

The extent of aggregation was scored on a scale of low, medium and high. Additionally the type of aggregation, if present, was recorded.

The quality of the suspension was scored on a scale of poor (p), poor-fair (p/f), fair (f), fair-good (f/g) and good (g).

Table I below gives the suspension properties of two types of lactose across a range of particle size. A is a sample of commercially available lactose. The particle size fractions were achieved by sieving commercially available lactose powders. The sieved diameters were taken to be substantially equivalent to the volume diameter. The median particle diameter of the fraction comprising < 38 μm particles of lactose is approximately 17 to 18 μm. The fraction comprising < 10 μm particles of lactose had a median particle diameter of about 2.5 to 3.0 μm.

Each example comprised a suspension of 0.83 w/w% of lactose powder and 99.17 w/w/% of HFA-134a, which is 1,1,1,2-tetrafluoroethane.

Table I

Example	Particulate Material	Size of Particle (µm)	Ease of Dispersion	Extent of Aggregation	Suspension Quality
A	lactose	4-400	g	low	f/g
B	lactose	>125	g	low	f
C	lactose	125-90	g	low	f/g
D	lactose	90-63	g	low	f/g
E	lactose	63-45	g	medium-flocculation	f
F	lactose	45-38	g	high-flocculation	p/f
G	lactose	<38	g	high-flocculation	p/f
H	lactose	<10	p/f	high-flocculation and irreversible aggregation	p
I	lactose - spray dried	>125	g	low	p/f
J	lactose - spray dried	125-90	g	low	f
K	lactose - spray dried	90-63	g	low/medium-flocculation	f/g
L	lactose - spray dried	63-45	g	medium/high-flocculation	p/f
M	lactose - spray dried	<45	g	high-flocculation	p/f

As can be seen from the results in Table I each type of lactose displayed good dispersion properties, apart from Example H, and at larger particle sizes low aggregation and at smaller particle sizes a varying degree of flocculation. The suspension quality varied across the size range of particulate lactose peaking for each type at mid-range sizes. Example H however exhibited aggregates which could not be dispersed by hand held shaking.

The variation in properties between the two types of lactose employed can be attributed to the different shape of the particles. The spray dried lactose comprised mainly spherical particles whilst the .... lactose comprised mainly ....

Table II below gives the suspension properties of two different particulate materials each of which has a particle size range of 125 to 90 μm. A suspension was formed with each particulate material with each of HFA-134a, which is 1,1,1,2-tetrafluoroethane, and HFA-227, which is 1,1,1,2,3,3,3 heptafluoropropane, as propellant.

<u>Table II</u>

Example	Particulate material (w/w%)	Propellant (w/w%)	Ease of Dispersion	Extent of aggregation	Suspension Quality
N	leucine (0.83)	HFA-134a (99.17)	g	medium-flocculated	g
O	leucine (0.71)	HFA-227 (99.29)	g	low/medium-flocculated	g
P	glucose (0.83)	HFA-134a (99.17)	g	medium-flocculated	f/g
Q	glucose (0.71)	HFA-227 (99.29)	g	medium-flocculated	f/g

Leucine is less dense than either of the propellants employed and had a tendency to cream i.e. rise to the surface of the propellant. Glucose is more dense than either of the propellants employed and had a tendency to sediment. In all cases however flocculated and other separated particulate material could be formed into a suspension on hand held shaking.

Examples R, S and T are comparative examples and demonstrate the suspension properties of a variety of particulate medicaments in the propellant HFA-134a in the absence of any second particulate material. The suspension properties measured by visual inspection were ease of dispersion, extent of aggregation and suspension quality and were scored as for Examples A to Q.

The results and compositions employed are given in Table III below.

Table III

Example	Particulate medicament (w/w%)	Median size of particle (μm)	Ease of dispersion	Extent of aggregation	Suspension quality
R	Salbutamol (0.08)	2.71	poor	high	poor
S	Salbutamol sulphate (0.08)	3.57	poor	high	poor
T	Budesonide (0.17)	1.83	poor	high	poor

Each of Examples R, S and T exhibited poor dispersion and poor suspension qualities. In each case the majority of the particulate medicament was present in about 20 aggregates, which could not be deaggregated by hand held shaking.

Examples 1 to 21 embodying the present invention

The metered dose inhaler shown in the accompanying drawing in diagrammatic form comprises an inverted container (1) and a metering valve (2). The inverted container (1) is capable of withstanding a pressure up to 6.895×10^5 Pa (100 psig) and is closed by a closure cap (3). The metering valve (2) extends through the closure cap (3) and includes a fixed volume chamber (4), a spring mechanism (5) biased to maintain the valve closed when not being actuated and an outlet stem (6) which opens into an expansion chamber (7). The container (1) and metering valve (2) are mounted by

support (8) in a holder (9) which is integral with an actuator tube (10) extending perpendicularly away from the holder (9). As can be seen in the drawing the expansion chamber (7) opens into the actuator tube (10). The container (1) contains the aerosol composition (11) comprising propellant and suspended particulate matter.

In use the container (1) is depressed relative to the holder (9) causing the chamber (4) to be open to the atmosphere and the fixed volume of liquefied gas therein to expand forcing the suspension into the expansion chamber (7) where the liquefied gas continues to expand and evaporate. The actuator tube (10) directs the aerosol so produced into the mouth or nose of the patient, as required, for inhalation.

Examples 1 to 7

Examples 1 to 7 demonstrate the suspension and aerosol properties for a range of compositions varying in the particulate medicament, the second particulate material having regard to both its particle size and its kind, and the propellant employed. In each of Examples 1 to 7 the particulate medicament is mixed together with the second particulate material by hand mixing in a mortar with a steel spatula at a ratio of particulate medicament to second particulate material of 1:10. The resulting mixture is dosed into the container of the metered dose inhaler described above, the closure cap crimped in place and the propellant added, as indicated in Table IV below.

The resulting suspensions are assessed visually for ease of dispersion, suspension quality and extent of aggregation and scored as above, as set out under Examples A to R. The results are given in Table IV below. The balance of each composition comprised the 1:10 mixture of the particulate medicament and the second particulate material.

Additionally, the shot weight and the aerosol characteristic of each suspension were assessed. The aerosol characteristics of each suspension were assessed using a 4 stage liquid impinger of Copley twin stage impinger operated at 60 L/min and the fine particle fraction, which provides an indication of the proportion of aerosol likely to

reach a patient's lungs, recorded. A score of at least 40% was marked as good (g), 30-40% as fair (f) and less than 30% as poor (p).

The shot weight i.e. the weight of suspension metered with each actuation of the valve, was assessed. In each case the shot weight was found to be reproducible indicating no adverse clogging or blocking of the valve mechanism.

Table IV

Example	Particulate medicament (μm)	Second particulate material (μm)	Propel-lant (w/w%)	Ease of Disper-sion	Extent of Aggregation	Suspension Quality	Fine particle fraction of aerosol
1	budesonide (1.83)	lactose (90-63)	HFA-134a (99.09)	g	low	f/g	f/g
2	salbutamol sulphate (3.57)	lactose (90-63)	HFA-227 (99.29)	g	low	f/g	g
3	salbutamol sulphate (3.57)	lactose (125-90)	HFA-227 (99.29)	g	low	f/g	g
4	salbutamol sulphate (3.57)	leucine (125-90)	HFA-113a (99.17)	g	medium-flocculated	f/g	g
5	salbutamol sulphate (3.57)	leucine (125-90)	HFA-227 (99.29)	g	medium-flocculated	f/g	g
6	salbutamol sulphate (3.57)	glucose (125-90)	HFA-134a (99.17)	g	low/ medium-flocculated	f/g	g
7	salbutamol sulphate (3.57)	glucose (125-90)	HFA-227 (99.29)	g	medium-flocculated	f/g	g

For each of Examples 1 to 7 the scores given in Table IV indicate a composition having acceptable suspension and aerosol properties. The flocculated material in each of Examples 4 to 7 could be dispersed by hand held shaking.

Examples 8 to 21

In each of the following Examples 8 to 21 commercially available lactose powder was employed as the second particulate material. The powder as received had a median volume diameter particle size of 80 μm. The range of volume diameter in the commercially available product was 4 to 400 μm.

The propellant employed in each of Examples 8 to 21 was HFA-134a which chemically is 1,1,1,2-tetrafluoroethane.

Examples 8 to 11 and Examples 13 and 20 contained salbutamol as a particulate medicament. The particulate salbutamol had a median aerodynamic diameter of 2.71 μm.

Examples 12, 14 to 19 and 21 contained salbutamol sulphate as a particulate medicament. The particulate salbutamol sulphate had a median aerodynamic diameter of 3.57 μm.

The particulate components of each of Examples 8 to 21 were dosed as indicated below and mixed together by hand mixing in a mortar with a steel spatula. The mixture was dosed as indicated below into a transparent container of a metered dose inhaler as described above, a metering valve crimped in place and the container filled with propellant as indicated below.

The suspensions so formed were assessed visually for ease of dispersion and suspension quality and each assessment was scored on a scale of poor (p), poor-fair (p/f), fair (f), fair-good (f/g), good (g).

The extent of aggregation of each suspension was also assessed visually and in each example was rated as low.

The shot weight i.e. the weight of suspension metered with each actuation of the valve, was assessed. In each case the shot weight was found to be reproducible indicating no adverse clogging or blocking of the valve mechanism.

The aerosol characteristics of each suspension of Examples 8 to 19 were assessed using a 4 stage liquid impinger or Copley twin stage impinger operated at 60 L/min and the fine particle fraction, which provides an indication of the proportion of aerosol likely to reach a patient's lungs, recorded. A score of at least 40% was marked as good (g), 30-40% as fair (f), and less than 30% as poor (p).

Examples 8 to 13 investigate the effect of the weight ratio of the particulate medicament to particulate lactose in the initial blend of particulate components by varying the ratio through the range 1:2.5 to 1:100. The overall composition in terms of the amount of propellant added was determined having regard to providing a therapeutic dose of medicament per actuation.

The compositions prepared and their attendant results in terms of ease of dispersion, suspension quality and fine particle fraction of aerosol are given in Table V below.

Table V

Example	Blend (wt%)	Propellant (wt%)	Wt. Ratio medicament: lactose	Ease of dispersion	Extent of aggregation	Suspension quality	Fine particle fraction of aerosol
8	0.29	99.71	1:2.5	f	low	f/g	g
9	0.91	99.09	1:10	g	low	f/g	g
10	2.15	97.85	1:25	g	low	f/g	g
11	4.21	95.79	1:50	g	low	f/g	f/g
12	6.77	93.33	1:67	g	low	f/g	f/g
13	8.35	91.65	1:100	g	low	f/g	f/g

As can be seen from Table V the ease of dispersion of the blend in the propellant increased as the proportion of particulate lactose to particulate medicament increased. At higher levels of particulate lactose to particulate medicament however the measurable fine particle fraction i.e. the particulate medicament of the aerosol decreased.

In the following Examples 14 to 19 the particle size of the particulate lactose was varied to determine its effect. Different size fractions of lactose were achieved by sieving the commercially available product, the sieved fractions were deemed to have particle diameter substantially equivalent to the volume diameter. The fraction comprising lactose particles <38 µm had a median particle size of approximately 17 to 18 µm. The mixture contained a weight ratio of particulate salbutamol sulphate to lactose of 1:10 and the mixture comprised in each instance 1.1wt% of the total composition with the balance comprising 98.90% propellant to give on each actuation a therapeutic dose of medicament. The results in terms of ease of dispersion, suspension quality and fine particle fraction of aerosol are given in Table VI below.

Table VI

Example	Particle size of material (µm)	Extent of aggregation	Ease of dispersion	Suspension quality	Fine particle fraction of aerosol
14	4-400	low	g	f/g	g
15	<38	low	g	g	-
16	38-45	low	g	g	f
17	45-63	low	g	g	f/g
18	63-90	low	g	f/g	f/g
19	90-125	low	g	f/g	f/g

Each of Examples 14 to 19 produced a suspension with good ease of dispersion properties. The suspension qualities were acceptable in all cases although were superior in the <38, 38 to 45 and 45 to 63 µm ranges. The aerosol properties however in terms

of fine particle fraction of medicament were better with particulate lactose of the greater particulate size.

In present Example 20 the fine particle fraction of aerosol tests were carried out on a metered dosed inhaler, as described above, containing the composition of Example 9 above to demonstrate the efficacy of the suspension throughout the life of an inhaler. The results are given in Table VII below in terms of shot nos. i.e. the counted actuations of the valve throughout the inhaler's life.

Table VII

Shot nos.	Fine particle fraction of aerosol
4-5	g
41-42	g
62-63	g

In present Example 21 the composition of Example 12 above was centrifuged at 5000g for 30 mins. The centrifuged suspension was observed to demonstrate a good ease of dispersion, a low extent of aggregation and a fair/good suspension quality. The test was designed to demonstrate the propensity or otherwise of the suspension to aggregate irreversibly or cake over time.

CLAIMS

1. Aerosol composition comprising a propellant and contained therein a first particulate material comprising particles having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material comprising particles having a median value diameter within the range 15 to 200 μm.

2. Composition according to claim 1 wherein the first particulate material has a median aerodynamic diameter within the range 1 to 10 μm, preferably within the range 1 to 5 μm.

3. Composition according to claim 1 or claim 2 wherein the second particulate material has a median volume diameter within the range 20 to 125 μm, preferably within the range 25 to 125 μm.

4. Composition according to any one of claims 1 to 3 wherein the weight ratio of first particulate material to second particulate material in the composition lies in the range 1:0.1 to 1:500, preferably in the range 1:5 to 1:50.

5. Composition according to any one of the preceding claims wherein the solubility of the first particulate material in the propellant is less than 49.9wt% with respect to the total weight of the substance present in the composition comprising the first particulate material present, preferably less 10 wt%, more preferably less than 1.0 wt%.

6. Composition according to any one of the preceding claims wherein the solubility of the second particulate material in the propellant is less than 49.9 wt% with respect to the total weight of the substance present in the composition comprising the second particulate material, preferably less than 10 wt%, more preferably less than 1.0 wt%.

7. Composition according to any one of the preceding claims wherein the composition comprises at least 80% wt and up to 99.999 wt% propellant, more preferably at least 90 wt% and up to 99.9 wt% propellant.

8. Composition according to any one of the preceding claims wherein the composition comprises at least 0.001 wt% and up to 20 wt% of the total of first and second particulate material present, preferably at least 0.1 wt% and up to 10 wt% of the total of first and second particulate material present.

9. Composition according to any one of the preceding claims further comprising a surfactant, flavouring material, buffer, preservative or any mixture thereof.

10. Composition according to any one of the preceding claims wherein the propellant is selected from chlorofluorocarbons, hydrofluorocarbons and mixtures thereof.

11. Composition according to claim 10 wherein the propellant is a hydrofluoroalkane selected from the 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and mixtures thereof.

12. Composition according to any one of the preceding claims wherein the second particulate material is selected from lactose, glucose, sorbitol, mono-, di-, tri-, oligo-, poly-, saccharides, amino acids, di-, tri-, oligo-, polypeptides and any physiologically acceptable derivatives, salts, forms and solvates thereof, and any mixtures thereof.

13. Composition according to any one of the preceding claims wherein the first particulate material is a medicament.

14. Composition according to claim 13 wherein the medicament is selected from salbutamol, salbutamol sulphate, terbutaline, terbutaline sulphate, ipratropium bromide or any physiologically acceptable salt or solvate thereof; budesonide, triamcinolone acetonide or any physiologically acceptable solvate thereof; peptides, proteins, nucleic acids or derivatives thereof; insulin, calcitonin, growth hormone, lutenising hormone releasing hormone, leuprolide, oxytocin or any physiologically acceptable salts or solvates thereof, or any mixture thereof.

15. Pharmaceutical composition comprising a propellant and contained therein a particulate medicament comprising particles having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material comprising particles having a median volume diameter within the range 15 to 200 μm.

16. A container containing a composition according to any one of the preceding claims wherein the container includes a valve outlet.

17. A container according to claim 16 wherein the valve outlet is a metered dose valve.

18. A container according to claim 17 in the form of a metered dose inhaler.

19. A method for preparing an aerosol composition according to any one of claims 1 to 15 comprising:-

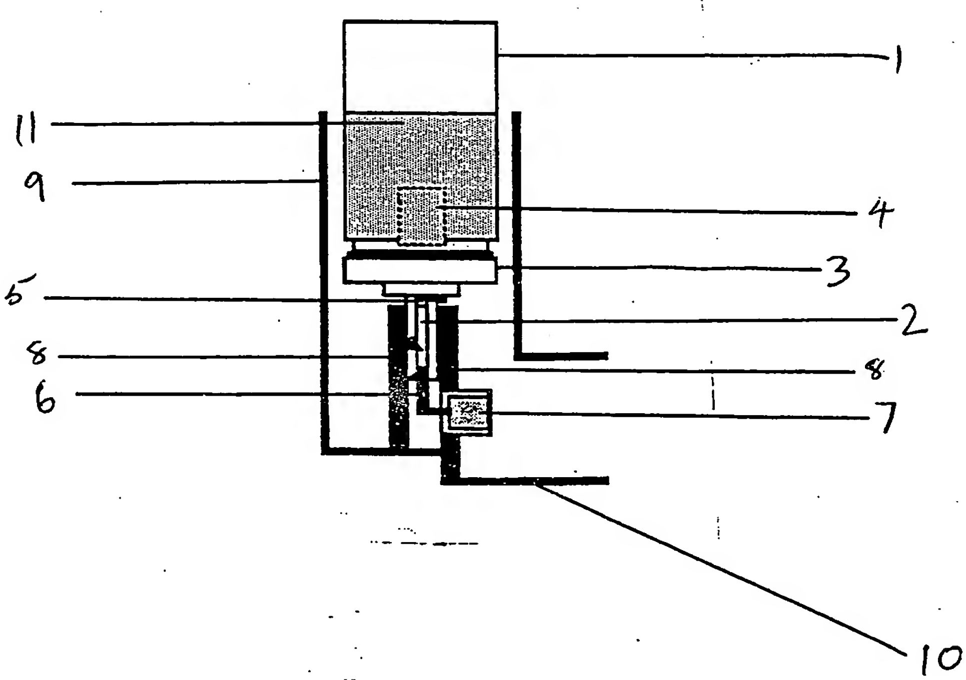
(a) forming a mixture of the first particulate material and the second particulate material;
(b) dispensing measured portions of respectively the said mixture and the propellant into a container; and
(c) sealing the container.

20. The method according to claim 19 wherein the mixture is dispensed into the container before the propellant.

21. The method according to claim 19 or claim 20 wherein the container includes an outlet valve, preferably a metered dose valve.

22. A mixture of a first particulate material having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material having a mean aerodynamic diameter within the range 15 to 200 μm.

23. A method of administering a particulate medicament to a patient in need thereof comprising forming an aerosol from the aerosol composition according to any one of claims 13 to 15 and the patient inhaling the aerosolised composition.



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